UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,795	12/05/2003	Ian Walters	011823-012510US	2275

20350 7590 01/09/2007
TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/729,795	WALTERS, IAN	
	Examiner	Art Unit	
	Zachary Skelding	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8-30-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

DETAILED ACTION

1. Applicant's Election, without traverse, filed September 28, 2006, is acknowledged.

   Claim 26 has been amended.

   Claims 1-26 are pending.

2. Applicant has elected, without traverse, the disease activity index species "MTWSI" and the additional agent species "methylprednisolone".

3. ***Claims 1-26 are under consideration*** as they read on a method for treating ulcerative colitis with anti-CD3 antibody wherein the disease activity index species is **"MTWSI"** and the additional agent species is **"methylprednisolone"**.

4. The instant application does ***not*** appear to be in sequence compliance as it refers to SEQ ID NOs: 1-3 throughout the specification, see page 11, 3rd paragraph for example, however a sequence listing does ***not*** appear to have been filed.

   Appropriate correction is required.

   See 37 CFR 1.821-1.825 and the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

5. The IDS filed August 30, 2004 has been considered by the examiner.

6. The instant claims appear to be entitled to the benefit of priority of USSN 60/431,649, filed **December 5, 2002.**

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

   Each letter of trademarked terms should be capitalized wherever it appears and each trademarked term should be accompanied by the generic terminology, e.g., ™ or ®. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

   The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

8. Claims 4 and 5 are objected to because they recite the ***abbreviations "MTWSI" and "MAYO"*** without writing out in full the meaning of these terms, which according to the instant specification stand for the "Modified Truelove and Witts Severity Index" and for "Mayo Scoring System for Assessment of Ulcerative Colitis Activity," respectively.

   Applicant is required to specifically recite the full phrase and the abbreviation to particularly identify the exact meaning of this abbreviation wherever it first appears in the claims, e.g., "Modified Truelove and Witts Severity Index (MTWSI)".

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   > The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 9-11 and 15-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. "M281" and "visilizumab": claims 15-19

Claims 15-19 are indefinite in the recitation of "M281 antibody" and "visilizumab" as the sole means of identifying these antibodies because "M281" is merely a laboratory designation and the term "visilizumab" does not clearly define this antibody in that artisans could use the same designation to define a completely distinct biological material, or in the alternative, could use a different designation to define the exact same antibody.

Applicant is invited to claim the antibody by the sequences that it is made of, i.e., the complete heavy and light chains. Alternatively, applicant is invited to recite an accession number for a deposit of a cell line/hybridoma that makes the claimed antibody. See 35 U.S.C. § 112, 1st paragraph, enablement rejection below.

B. "neutralizing" anti-CD3 antibody: claim 9

Claims 9-11 are indefinite in the recitation of "neutralizing" anti-CD3 antibody because the instant specification does not provide sufficient direction or guidance for the meaning of this term and the skilled artisan would not be certain of the meaning of this term without further guidance, i.e., are the claims directed to anti-CD3 antibodies that **"neutralize"** CD3 mediated T-cell receptor signaling, and therefore are "non-mitogenic", **OR** anti-CD3 antibodies that **"neutralize"** interactions between the CD3 transmembrane domains and the T-cell receptor transmembrane domains, **OR** anti-CD3 antibodies that **"neutralize"** the interaction between CD3 and CD8, or some combination of these possibilities?

Applicant is invited to amend the claim such that the metes and bounds are clarified.

C. Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the **"M291"** and **"visilizumab"** antibodies are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the pertinent cell lines/hybridomas which produce these antibodies. See 37 CFR 1.801-1.809.

With respect to **"M291"**, the instant specification at page 12, 1st paragraph discloses that, "[o]ther preferred antibodies include those that bind to the same epitope of CD3 as visilizumab...especially other ***humanized forms*** of **the M291 antibody** described in U.S. Patent No. 5,834,597." While U.S. Patent No. 5,834,597 discloses the variable heavy and light chains of "the M291 antibody" it does not appear to disclose the heavy and light chain constant regions; moreover, U.S. Patent No. 5,834,597 does not appear to indicate that the "M291" antibody has been deposited under the appropriate conditions with an appropriate storage facility. One of ordinary skill in the art would need to know/have access to the sequence of entire M291 antibody in order to make a "humanized M291 antibody" as claimed.

Therefore the instant specification does not put forth sufficient direction or guidance that the **"M291"** antibody is known and readily available to the public or obtainable by a repeatable method.

Applicant is invited to consider amending claim 15 to recite, "wherein said humanized antibody comprises a humanized heavy chain and a humanized light chain: (1) the humanized light chain comprising three complementarity determining regions..." as recited in claim 13 of U.S. Patent No. 5,834,597.

Moreover, with respect to **"visilizumab"**, The instant specification at page 11, 3rd paragraph discloses that **"visilizumab"** is a humanized ***form*** of the murine M291 antibody, and that the light chain variable, heavy chain variable and heavy chain constant regions of **"visilizumab"** correspond to SEQ ID NOs: 1, 2 and 3, respectively; however, the instant specification does ***not*** appear to disclose the sequence of the **"visilizumab"** ***light chain constant region***. Moreover, the instant specification does ***not*** appear to disclose that the **"visilizumab"** has been deposited under the appropriate conditions with an appropriate storage facility.

Therefore the instant specification does not put forth sufficient direction or guidance that the **"visilizumab"** antibody is known and readily available to the public or obtainable by a repeatable method.

Furthermore, it is noted that the instant specification at page 4, 2nd paragraph discloses **"visilizumab"** is also described in U.S. Patent No. 5,834,597.

However, the word **"visilizumab"** does not appear in U.S. Patent No. 5,834,597. Rather, U.S. Patent No. 5,834,597 discloses preparation of humanized forms of the murine M291 antibody, including disclosure of the use of human light chain constant region HF2-1/17 in the engineering of humanized forms of the M291 antibody. However, neither the instant specification, nor U.S. Patent No. 5,834,597 appear to provide sufficient direction or guidance that would lead one of ordinary skill in the art to ***the sequence*** of human light chain constant region ***HF2-1/17***. Moreover, ***it is further unclear*** whether **"visilizumab"** has a human light chain constant region identical to HF2-1/17 or if **"visilizumab"** comprises some ***variant of HF2-1/17***.

This rejection will be maintained until such time as applicant satisfies the requirements of 35 U.S.C. § 112, 1st paragraph, for example, by any one of the following routes:

(a) makes a deposit of the claimed antibody and provides assurances with regard to its public availability,

(b) amends the instant specification to recite the ***entire*** sequence of the claimed antibody, or

(c) clarifies for the record in some other way with respect to the requirements for the deposit of biological materials under 35 U.S.C. § 112, 1st paragraph, the ready public availability of the claimed antibody, or the exact sequence of the human light chain constant region used to make it, see MPEP 2400.

If applicant chooses option (a), i.e., to make a deposit of the claimed antibody, in addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the

deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit is made after the effective filing date of an application for patent, applicant should promptly submit a verified statement, ***from a person in a position to corroborate the fact***, that the biological material which is deposited is the same as the biological material specifically identified in the application as filed, i.e., is the same as the "visilizumab" antibody disclosed in the instant specification. This statement should be verified except if the person is an attorney or agent registered to practice before the Office, in which case the statement need not be verified. See MPEP 1.804(b).

Applicant is reminded that the mere reference to a deposit or the biological material itself in any document or publication does not necessarily mean that the deposited biological material is readily available. ***Even a deposit made under the Budapest Treaty and referenced in a United States or foreign patent document would not necessarily meet the test for known and readily available unless*** the deposit was made under conditions that are consistent with those specified in these rules, ***including the provision that requires, with one possible exception (37 CFR 1.808(b)), that all restrictions on the accessibility be irrevocably removed by the Applicant upon the granting of the patent.*** *Ex parte Hildebrand*, 15 USPQ2d 1662 (Bd. Pat. App. & Int. 1990). See M.P.E.P. § 2404.01.

13. **Claim 18 is rejected under 35 U.S.C. 112, first paragraph,** as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had **possession** of the claimed invention.

Claim 18 recites a method of treating ulcerative colitis comprising administering an antibody wherein: "said antibody is ***80% identical*** to an antibody that binds the same epitope as visilizumab".

However, the instant specification does not provide adequate written description of an antibody "***80% identical*** to an antibody that binds the same epitope as visilizumab" because relevant identifying characteristics for antibodies encompassed by this claim, such as structure or other physical and/or chemical characteristics, are not set forth in the specification as-filed.

Moreover, an antibody "***80% identical*** to an antibody that binds the same epitope as visilizumab" encompasses an extremely large number of amino acid sequence variants. Since the amino acid sequence of a protein determines its structural and functional properties the changes that can be tolerated in a antibody while retaining similar biological activity or structural specificity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function.

However, the instant specification does nto provide a sufficient description of the variant antibody speices that retain the biological activity or structural specificity of an antibody that binds the same epitope as visilizumab.

An exmxaple of how seemingly minor amino acid changes to an antibody can compromise its biological activity or structural specificity is provided by Chien et al., (Proc Natl Acad Sci U S A. 1989 Jul;86(14):5532-6), which describes how changing a single amino acid residue outside and distant from the antibody antigen binding site is nonetheless capable of completely eliminating antigen binding (see Chien, page 5536, 3rd paragraph). Chien concludes, "Our results and observations by others...suggest that residues distant from the binding site may play an important role in the specificity and affinity of the antigen-binding site." (see Chien, page 5536, 3rd paragraph).

Moreover, even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as taught by Rudikoff et al. (Proc Natl Acad Sci U S A. 1982 Mar;79(6):1979-83). Rudikoff teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

Thus, neither the instant specification nor the knowledge in the art are sufficient to extrapolate from a given antibody sequence, such as the visilizumab sequence to all other antibodies that bind the same epitope and are 80% identical, and thus one skilled in the art could not reasonably conclude that applicant had ***possession*** of the claimed invention.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page

1106 3rd column). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

"Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997).

The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim. Id. 43 USPQ2d at 1406.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 1115).

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:
A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

15. **Claims 1, 3-17 and 19-25 are rejected under 35 U.S.C. 102(b) as anticipated by** Tso et al. (U.S. Patent No. 5,834,597, cited in applicant's IDS of August 30, 2004) as evidenced by the Merck Manual of Diagnosis and Therapy (Mark Beers and Robert Berkow, eds., Published by Merck Research Laboratories, 17th ed., 1999, pages 302-313)(see entire documents).

It is noted for the purposes of prior art examination that the term "visilizumab", given its broadest reasonable interpretation consistent with the instant specification, is being read to encompass a humanized form of murine M291, wherein the light chain variable, heavy chain variable and heavy chain constant regions correspond to SEQ ID NOs: 1, 2 and 3, respectively, and wherein the light chain constant region is either a human light chain constant region identical to HF2-1/17 or some variant thereof (see, page 11, 3rd paragraph of the instant specification as well as section 12 above).

Tso teaches a method of treating inflammatory bowel disease in patient comprising administering an anti-CD3 antibody, more particularly chimeric, human or humanized anti-CD3 antibody, in particular, humanized M291 anti-CD3 antibody or humanized M291 comprising SEQ ID NOs: 6, 8 and 9, which correspond to SEQ ID NOs: 1, 2 and 3 of the instant application, and further comprising either a human light chain constant region identical to HF2-1/17 or some variant thereof, i.e., the "visilizumab" antibody (see entire document, in particular column 9, part III, the paragraph bridging columns 11-12, example 1, columns 12-15 and column 17, 1st paragraph through the end of column 20).

Tso further teaches anti-CD3 antibodies that neutralize CD3 in that they do not stimulate CD3 signaling, i.e., chimeric OKT3 antibodies with various mutations in their IgG2 constant region, which have affinities of at least 10^9/M. (see, in particular, columns 15-17, part 2 sections a-e and column 20).

It is noted that claims 21-24 recite administration of anti-CD3 at various dosages ranging from 10 ug/kg or lower to as high as 10 mg/kg, which given its broadest reasonable interpretation consistent with the instant specification, encompasses a unit of dose of 800 ug or less to 800 mg, based on an average weight of 80 kg (176 lbs) for the average ulcerative colitis patient.

Tso teaches various anti-CD3 antibody dosages that fall within the range encompassed by the instant claims (see, in particular column 12, 3rd paragraph).

Tso also teaches that a "therapeutically effective dose" of anti-CD3 antibody is "an amount sufficient to cure or at least partially arrest the condition and its complications," ***i.e., an amount sufficient to reduce symptom severity or cause disease remission*** (see, in particular column 12, 3rd paragraph).

Furthermore, as evidenced by the Merck Manual of Diagnosis and Therapy (see pages 302-312) the term "Inflammatory Bowel Disease" encompasses ulcerative colitis and Crohn's disease, which according to the Merck Manual are diseases that have significantly overlapping pathology, etiology, and treatments. Therefore, treating a patient with inflammatory bowel disease by administering an anti-CD3 antibody, for example the visilizumab antibody, would ***inherently*** encompass treatment of patients with ulcerative colitis.

Moreover, as further evidenced by the Merck Manual of Diagnosis and Therapy, all inflammatory bowel disease patients exhibit diarrhea as a symptom. Therefore, the use of anti-CD3 antibody in "an amount sufficient to cure or at least partially arrest the condition and its complications," would ***inherently*** reduce the MTWSI score, for example by reducing diarrhea, and if the dose given were sufficient to "cure" the condition, then the MTWSI score would have to be reduced by at least 75%.

Moreover, it is noted that when a reference teaches a sufficient small genus, such as the genus of Inflammatory Bowel Diseases which encompasses the ulcerative colitis and Crohn's disease species, the reference places the claimed species in the possession of the public. See In re Schaumann, 572 F.2d 312, 197 USPQ 5 (CCPA 1978).

Therefore, Tso, as evidenced by the Merck Manual of Diagnosis and Therapy anticipates the instant claims.

It is noted for the record that Tso further teaches that the effective dose is dependent upon "the severity of the condition and the general state of the patient's own immune system...", and that the dosage and scheduling of administration are ultimately "selected by the treating physician." (See, in particular, column 12, 3rd to 4th paragraphs). Therefore, the dosage of anti-CD3 antibody is a recognized results-effective variable, i.e., a variable that is recognized as important for therapeutic use of anti-CD3 antibody and is subject to optimization by routine experimentation by one of ordinary skill in the art, such a physician administering the claimed antibody to treat inflammatory bowel disease. See M.P.E.P. § 2144.05 II.B. and In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. **Claims 1-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over** Tso et al. (U.S. Patent No. 5,834,597, cited in applicant's IDS of August 30, 2004) in view of Lobb et al. (U.S. Patent No. 5,932,214), Rutgeerts et al. (Eur J Surg. 1998 Dec;164(12):911-5), Banerjee et al. (USSN 10/622,932) and Strom et al. (Therapeutic Immunology edited by Austen et al., Blackwell Science, Cambridge, MA, 1996; pages 451-456)(see entire documents).

The teaching of Tso are described above.

The claimed invention differs from the reference teaching in the ***explicit recitation*** of a particular disease activity index ("MTWSI"), in the treatment of ***severe steroid-refractory ulcerative colitis***, and in the further administration of ***methylprednisolone***.

Lobb teaches that "inflammatory bowel disease, or IBD, is a collective term encompassing ulcerative colitis and Crohn's disease..." Lobb further teaches the treatment of inflammatory bowel disease with anti-VLA4 antibody administered at a dosage sufficient to reduce symptoms/promote disease remission and that antibody dosages can be adjusted according to various factors known to the administering physician in order to achieve the desired amount of symptom reduction. Lobb also teaches that improvement in observed symptoms of an inflammatory bowel disease patient, such an ulcerative colitis patient, is measured by ***Truelove-Witts*** criteria or other disease activity indexes known in the art (see entire document, in particular column 1, 3rd paragraph, column 5, 2nd-3rd paragraphs, and column 8, 4th paragraph).

Rutgeerts teaches alternative treatments for inflammatory bowel disease patients who are refractory to corticosteroids such as various biotherapeutics, including anti-TNFα antibody (see entire document, in particular page 911, left column and page 914 "cytokines and anticytokines").

Banerjee teaches administration of methylprednisolone in conjunction with anti-TNFα antibody to treat inflammatory bowel disease and/or Crohn's disease (see entire document, in particular page 27, paragraphs [0323]-[0327] and page 34, paragraph [0389]).

Strom et al. teaches that it was known and practiced by the ordinary artisan to employ a multitiered approach to immunosuppressive therapy similar in principle to that used in chemotherapy, several agents are used simultaneously, each of which is directed to a different molecular targets. Additive-synergistic effects are achieved through application of each agent at relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect (see entire document, including the introduction on page 451).

One of ordinary skill in the art would have been motivated to combine these teachings to practice the claimed invention, and would have had a reasonable expectation of success in doing so, because a person of ordinary skill in the art, such as a physician, treating inflammatory bowel disease (which encompasses treatment of ulcerative colitis as taught by Lobb) with an anti-CD3 antibody as taught by Tso, would have been motivated to use a standardized measure of treatment efficacy, such as the MTWSI taught by Lobb, to facilitate dosage optimization so as to "cure" patients of the inflammatory bowel disease as taught by Tso, and in so doing decrease their MTWSI score by at least 75%.

Moreover, one of skill in the art would been motivated to treat inflammatory bowel disease patients who are refractory to corticosteroids with the anti-CD3 antibodies of Tso because as taught by Rutgeerts, patients with refractory inflammatory bowel disease on steroid therapy are "frustrated" because alternative treatments, such as standard immunosuppressants carry toxicity and neoplasia risks, and so newer, more targeted treatment options, such as biotherapeutics, including anti-TNFα, are desirable.

One of ordinary skill in the art would have been further motivated to treat steroid-refractory ulcerative as taught by Rutgeerts a non-steroidal therapeutic, such as the anti-CD3 antibodies as taught by Tso, in the hope that by simultaneously combining several agents directed at different molecular targets, as taught by Strom, for example anti-CD3 in combination with a corticosteroid, one could achieve additive-synergistic effects that overcome the steroid resistance.

Furthermore, one of skill in the art would have been motivated to treat inflammatory bowel disease patients, with the anti-CD3 antibodies as taught by Tso, in combination with the corticosteroid methylprednisolone because, as taught by Strom, combination therapies involving immunosuppressants such as the agents employed in the instant claims allow for additive-synergistic effects through application of each agent at relatively low dose, thereby limiting the toxicity of each individual agent while increasing the total immunosuppressive effect, and as taught by Banerjee, it is advantageous to combine methylprednisolone with a biotherapeutic agent, such as anti-TNFα antibody, to treat inflammatory bowel disease.

One of ordinary skill in the art would have been further motivated to combine anti-CD3 antibody with a corticosteroid, such as methyprednisolone, to treat ulcerative colitis because as taught by Rutgeerts, traditionally corticosteroids have been successfully used for initial treatment of inflammatory bowel disease.

Finally, it would have been prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose since the idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention.

18. No claim is allowed.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary Skelding whose telephone number is 571-272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding, Ph.D.
Patent Examiner
December 21, 2006

PHILLIP CAMBEL, PH.D
PRIMARY EXAMINER

12/21/06
TC 1600